IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Pouletty	Art Unit: 1806
Serial No. 08/254,299	Examiner: R. Schwadron
Filed: June 6, 1994	Atty's Docket No.: A-55320-1/BIR SANG-13-2
For: *Cytomodulating Conjugates of Members of Specific Binding Pairs*	Palo Alto, CA

DECLARATION UNDER 37 C.F.R. §1.132

The Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Jean-Paul Soulillou, do hereby declare as follows:

I am a member of the faculty of the Centre Hospitalier, Regional de Nantes. My curriculum vitae accompanies this declaration. I have read and understood the contents of the Office Actions dated June 27, 1995 and February 6, 1996, the responses to those office actions, and the Declaration by Dr. Alexander Lussow.

In the Office Action of February 6, 1996, the Examiner states in regard to the Lussow Declaration that, "... it is well known in the art that rodent models for the study of transplantation do not produce results that are readily applicable to humans and are therefore not predictive of whether particular agents can be used in vivo for the treatment of transplant rejection in humans". This proposition is supported by a reference to Tueveson *et al.* (1993) Immunological Review **136**:99.

Tueveson *et al.* state on page 100 that "a main problem in the rodent model . . . is the ease with which rejection is usually suppressed". However, even if this statement is true, this phenomenon does not imply that a drug shown to be active in these models will not also be active in the human immune system. In fact, the

concordance between an action on the immunity of rodents and humans is almost a rule in the field of bioreagents, and has justified the use of these models as a second step of screening bioreagents such as IL-2 receptor, anti-LFA-1, CTLA4Ig, *etc.*, as well as drugs such as cyclosporine A, FK-506, *etc.*

The rodent model is generally accepted in the field as a screen for immunosuppressant drugs, as described by Tueveson *et al.* The data from this model are generally accepted as useful in encouraging further use of the candidate drug in higher mammals, including humans. The rodent model provides an indication of the dosage range to be used in humans. The absence of a direct correlation does not mean that the rodent model does not provide the basis for continued development of the candidate drug. The rodent model indicates that the drug is immunosuppressive, is probably safe, and warrants further investigation. Therefore, in my opinion the rodent model is used to predict a candidate drug's behavior in humans, even if it is not perfect in its predictability.

Second, the present invention is concerned with a drug that differs from the drugs with which Tueveson *et al.* is concerned. The subject drugs act as a bridge between activated T cells and a cytotoxic system. The rodent model has a very similar T cell population and complement system to humans. Since it is these aspects that are involved with the subject drugs, it would be expected that the rodent model would be a better predictor in this case than in cases where one was dealing with a synthetic molecule as the candidate drug. The process of binding to T cells and complement cytotoxicity is expected to be analogous for the two species.

The example of conjugates that bind to a target secondarily recognized by an "endogenous" effector seems to me to clearly belong to the family of bioreagents-type compounds, since the target is precisely individualized. Again, this is in the family of compounds where the rodent model has been most

predictive. The treatment should clearly be effective on the same target cells, in the subject invention activated human T cells.

As a last point with respect to Tueveson *et al.*, I have found the reference to be surprisingly weak. It is an invited paper, and peppered with unproven statements. As a member of the editorial board of several journals, I can firmly say that I would have immediately refuted such a paper, even for a review. In contrast, hundreds of first class works have first demonstrated in rodents the immunosuppressive property of a molecule that has been active in other species.

So far as Borrebaeck et al. (1993) Immunology Today 14:477, while rodent antibodies would be expected to have the α-gal epitope, removal of sugars is quite feasible using endo- and exoglycosidases. A large number of rodent monoclonal antibodies have been administered to humans and in many cases with positive effect. Therefore, it may be that the α-gal is not active when present on the antibodies, or the α-gal is not present on the monoclonal antibodies. Whatever the reason, the α-gal epitope has not been reported to be a problem, particularly when used in conjunction with a regimen involving other immunosuppressants.

Finally, Waldeman and Harris are cited for the proposition that rodent monoclonal antibodies are not useful for human therapies. Under a variety of conditions, such monoclonal antibodies are useful. For transplantation, it is the initial few days that are of greatest concern. If one can enhance the potential for survival of the graft, this can be very important. Since many of the drugs used today have serious side effects, by being able to reduce the levels of such immunosuppressant drugs in the first days after the transplant, and thus reduce the debilitating effects of such drugs, this is very helpful to the patient and the management of the transplant. A single dose of the monoclonal antibody is not likely to induce an immune response. Further doses should also be permissible, in view of the immunosuppressed state of the patient.

In my expert opinion, the rodent model supports the continued development of the subject invention for transplants and provides a reasonable degree of confidence of anticipated success in humans.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dr. Jean-Paul Soulillou

21 May 1996.

Date